

Department of Health and Human Services
Food and Drug Administration
Docket No. 2005N-0038
Reporting of Adverse Events to Institutional Review Boards; Public Hearing

Comment from Chesapeake Research Review, Inc.
April 21, 2005

In response to FDA's announcement of a public hearing to consider the process by which institutional review boards (IRBs) obtain and review information on adverse events that occur during the conduct of clinical investigations, Chesapeake Research Review, Inc. (CRRI), an independent IRB located in Columbia, Maryland, respectfully submits the following comment.

As background, CRRI's IRB regularly reviews multi- and single site human subjects research inclusive of drug/device/biologic studies. CRRI's IRB requires submission of serious and unexpected adverse events (SAEs) regardless of the relationship to the test article and does not require nor review expected adverse events that do not involve risk to human subjects or others. CRRI also requires submission of unanticipated adverse device effects (UADEs) per the device regulations. Due to CRRI processes, please note that the terminology that will be used in this comment differs slightly than that used in the presentations at the public hearing. Internal SAEs refer to the individual reports submitted from sites which CRRI oversees that are serious and unexpected adverse events. External SAEs refer to the individual reports submitted from sites which CRRI does not oversee that are serious and unexpected adverse events.

CRRI provides the following comment on the 3 issues outlined in Section III of the Federal Register Notice:

1. The role of IRBs in the review of adverse event information from ongoing clinical trials.

What role should IRBs play in the review of adverse event information from an ongoing clinical trial?

The IRB's role should be that of an ethics committee that reviews aggregate, analyzed SAE and relevant AE information that is accompanied by recommendations regarding (1) whether or not the clinical trial should continue and (2) if so, whether the IRB should require a change in the study procedures or the informed consent document. The IRB would then have sufficient information to determine whether or not this information

affects the risk:benefit ratio of the clinical trial, determine whether or not this information affects the continued conduct of the clinical trial, and determine if this information needs to be communicated to subjects (as it may affect their willingness to continue participation in the research) and the most appropriate method of communication.

How does that role differ from the current role of IRBs?

The primary difference is the completeness of the information available to the IRB. The FDA Information Sheets for Institutional Review Boards and Clinical Investigators suggest that IRBs should prepare written procedures outlining how they will review adverse events, but do not specify which events must be reviewed.

In the absence of specific guidance, most IRBs have created their own “system” to handle adverse events information. The variety and variability in such systems across IRBs has created an inconsistent and misleading expectation of what the IRB’s role is with regard to adverse events information and human subject protections. Some IRBs look at individual SAE reports and analyze relatedness determinations, other IRBs will determine whether or not changes need to be made to Informed Consent Forms based on an individual internal or external SAE report, while other IRBs will do trend analysis of internal and external SAEs to determine whether or not there is a safety issue/concern. There is no consistency in the types of information that IRBs receive nor is there consistency in what IRBs are doing with the information once they get it. Therefore, there is often confusion about what the role of the IRB is when it comes to adverse events information.

In general though, most IRBs serve as a safety data review committee with regard to adverse events information. Often times, the current role of an IRB is to receive individual internal and external SAE reports and “analyze” and “assess” these individual events and make a determination as to whether or not the event impacts the safety of subjects or is a risk to subjects. IRBs are not constituted, nor is it appropriate for IRBs, to “analyze” and “assess” these individual events in order to make these types of determinations. Since IRBs have a diverse membership that includes individuals with scientific and non-scientific backgrounds, it is inappropriate to ask IRBs to “analyze” and “assess” individual events. In addition, IRBs are not given complete and sufficient information that is needed to make informed determinations about the impact of such events on the safety of subjects.

Should IRB responsibilities for multi-site trials differ from those for single-site trials? If so, how should they differ?

No, the IRB’s responsibilities when it comes to adverse events information should not differ for multi-site vs. single-site trials because in both multi- and single studies, the sponsor is still the ultimate holder of all adverse events information, not the IRB.

An additional thought to consider is that IRB responsibilities and considerations may differ based on sponsorship of the research (industry vs. investigator) rather than by

number of sites (multi vs. single). For example, an IRB may have different requirements (i.e. more stringent, require an independent 3rd party to be involved) for a trial's safety monitoring plan if the trial is investigator-initiated vs. industry sponsored.

2. The types of adverse events about which IRBs should receive information.

What types of adverse events should an IRB receive information about, and what types of information need not be provided to IRBs?

IRBs should receive aggregate, analyzed SAE and relevant AE information that is accompanied by recommendations. In addition, it should be defined in the protocol and/or Investigator's Brochure what adverse events are expected, related to the indication, usual progressions, etc. so that IRBs can use this information during the review of the aggregate, analyzed information and recommendations. IRBs should not receive any individual SAE (internal or external) or AE reports.

In addition, if the sponsor and/or investigator determines that SAE and/or relevant AE information should result in a protocol, Informed Consent, or Investigator's Brochure modification, then the report(s) should be submitted with the proposed modification to the IRB to be taken into consideration as the rationale for the proposed modification. If there is an apparent immediate hazard to the study subjects, the clinical investigator can impose a change necessary to protect the welfare of the study subjects without IRB review, as provided by 21 CFR 312.66.

As stated in the Federal Register Notice, there is a general consensus in the IRB community that adverse event reports submitted individually and sporadically throughout the course of a study without any type of interpretation are ordinarily not informative to permit IRBs to assess the implications of reported events for study subjects. CRR believes this to be true which is why it is CRR's opinion that IRBs should not receive any individual SAE (internal or external) or AE reports.

In addition, there is no specific guidance for 'timeliness' of submission of adverse events information to IRBs, thus subject protection is not well served in the current model because others (such as investigators and sponsors) have this information in advance of IRBs. It would seem that the parties that initially receive adverse events information would be the logical point to do the initial severity analysis and monitor trends.

In a multicenter study, should the criteria for reporting adverse events to an IRB differ, depending on whether the adverse events occur at the IRB's site or another site?

No. IRBs should not receive any individual SAE (internal or external) or AE reports. One of the biggest problems that IRBs face with regard to adverse events information is how to evaluate the individual reports that lack complete information. For multicenter studies, regardless of what is reported to the IRB (internal vs. external SAEs), the IRB never has more than a small piece of the big picture. It is the sponsor that has all of the safety information (AEs and SAEs) for both the individual study as well as other studies

and uses of the test article and is best suited to analyze events and communicate any safety concerns.

3. **Approaches to providing adverse events information to IRBs**

If prior to submission to an IRB, adverse event reports were consolidated or aggregated and the information analyzed and/or summarized, would that improve an IRB's ability to make useful determinations based on the adverse event information it receives?

Yes. Aggregate and analyzed SAE and relevant AE information would greatly improve an IRB's ability to make useful determinations. However, it is important to emphasize two other points:

1. The information should be accompanied by an assessment of how this information affects the ongoing trial as well as recommendations for changes in the trial procedures or the informed consent.
2. IRBs would still need guidance from federal agencies (FDA/DHHS) as to what the IRB's role is in reviewing this information and the types of determinations they should be making based on this information.

When should consolidated reports be provided to IRBs?

The interval for providing consolidated reports would probably vary by trial. The interval should be governed by the safety monitoring plan devised by the sponsor. At a minimum, the reports should be available to the IRB at the time of continuing review.

Who should provide such reports?

It would be most appropriate for the sponsor of the trial to provide the reports. The sponsor could provide the reports directly to the IRBs, as is provided for in the device regulations at 21 CFR 812.150(a)(1).

Should the approach to providing IRBs adverse event reports be the same for drugs and devices?

Yes. The more consistency there is between the requirements for drugs and devices, the less confusion there will be among the research community. The terminology, the information that is to be provided to IRBs, and the time limits for providing the information should be made consistent. An example of current inconsistency is the device regulations generally specifying "working days" whereas the drug/biologic regulations specify "calendar days."

Summary and Recommendations

In summary, CRR would like to emphasize that irrespective of the diverging recommendations presented at the public hearing on March 21, 2005, it is in the best interest of research subjects when FDA, sponsors, clinical investigators and IRBs work in

concert to decrease the regulatory and administrative burden that IRBs currently carry specifically with regard to management of adverse events information for clinical trials. When IRBs receive comprehensive information, supported by appropriate data, the IRB is then able to discharge its duties to provide oversight for the protection of the rights and welfares of research participants.

In addition to the specific comments outlined above, CRRI emphasizes that the current system could be greatly improved in the short run if FDA would provide more detailed guidance. Here are the specific questions that CRRI has identified as needing guidance from FDA:

1. WHAT adverse events information must go to the IRB (i.e. AEs, internal SAEs, external SAEs, individual reports, summaries)?
2. WHEN should adverse events information be sent to the IRB (i.e. promptly, as soon as possible, within 10 working days, within 7 calendar days, at the time of continuing review)?
3. WHO should send adverse events information to the IRB (i.e. sponsor, investigator)? If the sponsor has the responsibility of sending the reports to the IRB, it should be made clear the investigator no longer has that responsibility in order to eliminate duplicative reporting.
4. WHAT is the IRB being tasked with in reviewing the adverse events information (i.e. what determinations should the IRB be making)? For example, should an individual IRB require changes in the protocol that may affect only one site of a multi-site study?
5. HOW should the IRB interact with both the investigators and sponsors with regard to adverse events information?

Protecting human subjects who participate in clinical trials is a shared responsibility. Per the regulations, clinical investigators, FDA, DMCs, and IRBs all have responsibilities when it comes to adverse events information. However, the role of the IRB is the least well defined in the regulations, which has led to the current regulatory and administrative burden on the IRB. Any solution to this problem must start with clear guidance from the FDA outlining the role and responsibilities of the IRB with regard to review and management of adverse events information.

CRRI thanks FDA for the opportunity to comment.

Respectfully submitted,
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